Section III (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, claims 2, 10, 13 and 19 have been amended. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

Specifically, support for the amendments to claim 10 is provided in the specification at page 6, line 30 to page 7, line 2 at page 8, lines 6-8 and at page 9, line 4. Support for the amendment to claim 13 is provided in the specification as originally filed, specifically the Sequence Listing and by Exhibits A and B provided hereto. Claims 2 and 19 have been amended simply to correct the dependency, in light of the cancellation of claims from which those claims previously depended.

Claims 1, 4-9, 14-18 and 20 have been cancelled without prejudice.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application.

Thus, upon entry of the amendments, claims 2, 3, 10-13, 19 and 21-22 will be pending, of which claims 2, 3, 11, and 12 are withdrawn.

B. Request for Rejoinder of Withdrawn claims 2, 3, 11 and 12

In the Office Action mailed February 3, 2009 the examiner has withdrawn claims 2, 3, 11 and 12 "as being drawn to a nonelected invention…" The Office Action mailed July 9, 2008 contained a Requirement for Election among species, not a Requirement for Restriction among inventions. The examiner has stated that there is no allowable generic or linking claim. Applicants respectfully disagree.

Claim 10 is a generic claim, encompassing a scaffold for tissue engineering applications, which has a cell adhesion peptide and/or tissue growth factor-derived peptide immobilized on the surface. Claim 10 is generic to inclusion of each of cell adhesion-inducing peptides and/or tissue growth factor-derived peptides.

Part I of the species requirement in the Office Action mailed July 9, 2008 required selection of a single species of "the proteins listed in Claim 4 or Claim 13." However, no reference was made

to claim 1 or to dependent claims 2 and 3 or 11 and 12. Applicants were not provided with an option to select the cell adhesion-inducing peptide in general or the specific peptides of claims 2, 3, 11 or 12.

Claims containing non-selected species should not be withdrawn, but should be held in abeyance during the term of examination of the selected species. It is understood that in a species election, if any species is found to be allowable, that an additional species will be examined, until all species have been examined. i.e., all cell adhesion-inducing peptides and all tissue growth factor-derived peptides and all combinations thereof. If any generic claim is finally held to be allowable, all claims drawn to species containing all elements of the generic claim will also generally be held to be allowable. (MPEP § 806.04(d)).

Acknowledgement of the status of claims 2, 3, 11 and 12 as claims under examination is requested. However, in Section I above, claims 2, 3, 11, and 12 are labeled with a "Withdrawn" status identifier, in deference to the status identified by the examiner in the Office Action mailed July 9, 2008.

C. Objections to the Specification

In the Office Action mailed February 3, 2009, the examiner has made objections to the specification based on "a lack of correspondence between the discussion of the fragments and the sequences appearing in the Sequence Listing…" In response, Applicants provide herein various amendments to the specification and a replacement Sequence Listing. No new matter is added by such amendments. As amended, the sequences identified in the specification are consistent with the Sequence Listing.

Specifically the following amendments have been made:

SEQ ID NO:	Description of Amendment	Support
3	Amended in Sequence Listing to properly reflect length as 17 aa long (residues 2-18 of BMP-2)	Specification, p. 4, ll. 21-23 Exhibit A
4	Amended in Sequence Listing to properly reflect length as 17 aa long (residues 2-18 of BMP-4)	Specification, p. 4, ll. 21-23 Exhibit B
5	Amended in Sequence Listing to properly reflect length as 17 aa long (residues 2-18 of BMP-6)	Specification, p. 4, ll. 21-23 Exhibit C

6	Amended in Sequence Listing to properly reflect length as 17 aa long (residues 24-40 of BMP-2)	Exhibit A
7	Amended in Sequence Listing to properly reflect length as 25 aa long (residues 47-71 of BMP-2)	Specification, p. 4, l. 25 Exhibit A
11	Specification amended to properly identify peptide as residues 355-374 within BMP-2	Sequence Listing, SEQ ID NO: 11 Exhibit A
15	Specification amended to properly identify peptide as residues 366-386 within BMP-4	Sequence Listing, SEQ ID NO: 15 Exhibit B

Exhibits A, B, C and D provide FASTA sequences for each of BMP-2, BMP-4, BMP-6 and BMP-7, respectively. As a specific example in the Office Action mailed February 3, 2009, the examiner noted that the indicators of sequence length for SEQ ID NO: 6 were inconsistent between the specification and the Sequence Listing. As amended elected SEQ ID NO: 6 is consistently referred to as residues 24-40 of BMP-2 and 17 amino acids long.

Withdrawal of the objection is respectfully requested.

D. Objections to the Claims

In the Office Action mailed February 3, 2009 the examiner objected to claims 1 and 10 for containing the language "have" where they should recite "has." The examiner's attention is respectfully drawn to Section II above, where claim 1 has been cancelled and claim 10 has been amended in accordance with the examiner's suggestion. Withdrawal of the objection is respectfully requested.

E. Rejection Under 35 U.S.C. §112, second paragraph

The examiner also rejected claims 4 and 13 under 35 U.S.C. §112, second paragraph as indefinite due to the uncertainty with regard to SEQ ID NO: 6. As set forth in detail above, SEQ ID NO: 6 has been clarified as residues 24-40 of BMP-2 and 17 amino acids long. This sequence is the elected sequence.

Withdrawal of the rejection is respectfully requested.

F. Priority

By the Office Action mailed February 3, 2009, priority to Korean Patent Application 10-2004-0019010 was denied, as the application is in Korean and therefore, the examiner could conduct only a limited review of the application. The Examiner's attention is respectfully drawn to Exhibit E hereto, where a translation of selected paragraphs of Korean application 10-2004-0019010 and a Verification of such translation is provided.

By the translation of relevant paragraphs of Korean application 10-2004-0019010, description of various cell adhesion-inducing peptides is provided, such as the amino acid sequences of RGD, SEQ ID NO: 1 and SEQ ID NO: 2 of the present application, and the tissue growth factor-derived peptides such as the amino acid sequences of SEQ ID NOs:10-12 of BMP-2, SEQ ID NOs: 14-16 of BMP-4, SEQ ID NOs: 18-20 of BMP-6 and SEQ ID NOs: 22-24 of BMP-7 and the peptides described at pages 5-6 of the application at paragraphs (b)-(j), and provided in the Sequence Listing of the present application as SEQ ID NOs: 25-69.

To the extent that support for the claims is present in Korean application 10-2004-0019010, priority to the application is claimed.

G. Rejection of Claims Under 35 U.S.C. §103

Claims 1, 4, 7, 10, 13, 16, 17 and 18 are rejected in the Office Action mailed February 3, 2009 as obvious under 35 U.S.C. §103 over U.S. Patent No. 6,409,764 (hereinafter "White et al.") and further in view of PCT Publication WO 2005/113585 (hereinafter "Knopf et al."). Applicants respectfully traverse the rejection.

Of the rejected claims, claims 1, 4, 7, 16, 17 and 18 have been cancelled. The rejection is discussed below as it is relevant to pending and amended claims 10 and 13.

The examiner's attention is respectfully drawn to amended claim 10 above. As amended, the claim recites a scaffold with the characteristics of: 1) immobilization of the peptide on the scaffold in an amount of 0.1-10 mg/cm^2, 2) addition of CGC spacer at the N-terminal end of the tissue growth factor-derived peptide, 3) the scaffold is an implant and the surface of the implant

is modified by oxidation and nitrification to facilitate the adhesion of the active peptide to the surface. The cited combination of prior art does not disclose such a scaffold.

Specifically, neither of White et al. or Knopf et al. describe a scaffold with the recited characteristics of applicants' invention. Furthermore, in the discussion of White et al., the examiner alleged that "'764 teaches a bone graft material or scaffold for tissue engineering applications comprising BMP-2 immobilized on the surface." While the examiner further acknowledged that "'764 does not teach immobilizing a fragment of BMP-2, namely, elected SEQ ID NO: 6..." The examiner cites Knopf et al. as "teach[ing] exactly this fragment..." However, the combination of White et al. and Knopf et al. fails to provide additional aspects of applicants' claimed invention.

Traditional methods include simple application of tissue growth factors to bone graft materials used in guided bone regeneration and polymer scaffolds used in tissue engineering so as to induce sustained release of the tissue growth factors. However, there is a disadvantage in that, with these bone graft materials or scaffolds themselves, the tissue growth factors are physically mixed, so that, in initial application, **the burst release of the growth factors occur, thus making it difficult to maintain the tissue growth factors at an effective concentration for a treatment period.**

By contrast, the present inventors have made extensive efforts to solve the above-described problems occurring in the prior art, and consequently found that **a bone graft material and scaffold having a surface immobilized with the active site peptides of a tissue growth factor and an extracellular matrix protein, which can achieve a tissue regeneration effect, show stable and lasting pharmacological effects,** even with a low concentration of the peptides. On the basis of this finding, the presently claimed invention was developed, as recited in claim 10.

Fig. 6 and Fig. 8 of White et al. are reproduced below, where 12 is a TP device, 69 is TGF-β and 67 is a matrix:

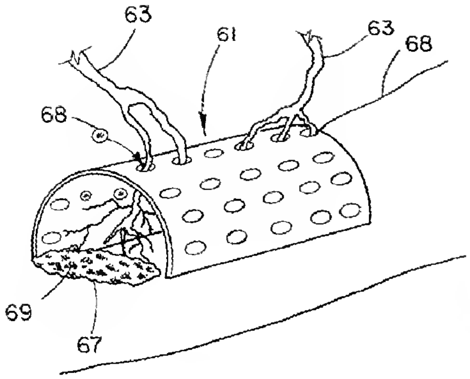

FIG. 6

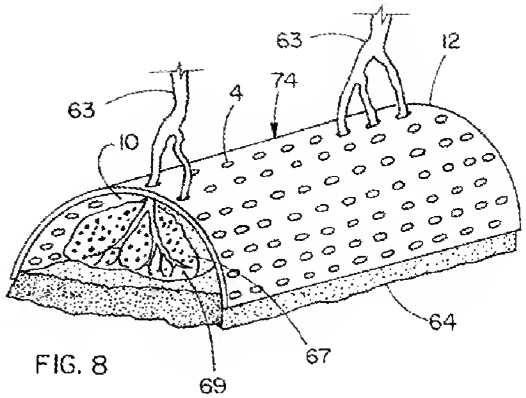

FIG. 8

In the methods and materials of White et al., as can be seen in the above drawings and in claims 1, 16, 21, 23, 38-43, 46 and 59-63 of White et al., TGF-β proteins are merely placed in a space with tissue penetrable device (TP device), not immobilized on the surface of implant, scaffold, etc. Accordingly, White et al. still has the above problems of a "burst effect" and provides a system with which it would be difficult to maintain the tissue growth factors at an effective concentration for a treatment period. Additionally, White et al. require a carrier substance or a matrix material which can contain the TGF-β protein.

Accordingly, the combination of White et al. and Knopf et al. fails to render the scaffold of claim 10 obvious. Claim 13 is of dependent form under claim 10, and correspondingly distinguished over the art.[1]

Based on the foregoing, White et al. in view of Knopf et al. fails to provide any logical basis for the scaffold recited in claims 10 and 13. White et al. in view of Knopf et al. <u>does not</u> render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 10 and 13 under 35 U.S.C. §103 as being obvious over White et al. in light of Knopf et al. is respectfully requested.

Claims 5, 6, 8, 9, 14, 15 and 20-22 are rejected in the Office Action mailed February 3, 2009 as obvious under 35 U.S.C. §103 over White et al in view of Knopf et al. and further in view of Gavreau et al., *Bioconjugate Chem.*, 15:1146-1156 (2004) (hereinafter "Gavreau et al.") and U.S. Patent No. 6,316,003 (hereinafter "Frankel et al."). Applicants respectfully traverse the rejection.

[1] If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). (MPEP §2143.03)

Of the rejected claims, claims 5, 6, 8, 9, 14, 15, and 20 have been cancelled. The rejection is discussed below as it is relevant to pending claims 21 and 22.

As set forth above in detail, the combination of White et al. and Knopf et al. fails to render the scaffold of claim 10 obvious. Claims 21 and 22 depend from claim 10. Citation of Gavreau et al. and Frankel et al. fail to remedy the deficiencies of the combination of White et al. and Knopf et al.

Specifically, the examiner cited Gavreau et al. as "discuss[ing] the use of sulfo-SMCC to achieve cross-linking of a cysteine-containing protein to a solid substrate in order to immobilize the protein ...[and] oxidation and nitrification to facilitate adhesion of proteins to solid supports." (Office Action mailed February 3, 2009, p. 8.)

As provided above and in Exhibit E hereto, paragraph <35> of priority Korean application 10-2004-0019010 provides:

> <35> As the barrier membrane to be surface-activated by the present invention, all kinds and types of barrier membranes can be used if they are used in the technical field. Pre Preferred examples of these barrier membranes include porous membranes made of polylactic acid, regeneraton membranes made of nanofibers of chitin or chitosan, and film-shaped barrier membranes made of chitin or chitosan. Also, as the implants, titanium implants are preferably used but are not limited thereto. In this respect, the surface of the implants is preferably <u>modified by oxidation and nitrification so as to facilitate the adhesion of the active peptide to the surface</u>. (Emphasis added)

The claimed element of the surface modification, as recited in claim 10, from which claims 21 and 22 depend, is clearly supported in the priority Korean application, which has a filing date of March 19, 2004. As such, the cited reference Gavreau et al., published August 20, 2004 is not prior art to the claimed invention.

Therefore the rejection of claims 20 and 21 over the combination of White et al., Knopf et al. Gavreau et al. and Frankel et al. is moot. Withdrawal of the rejection is respectfully requested.

Additionally, claim 19 is rejected as obvious under 35 U.S.C. §103 over White et al in view of Knopf et al. and further in view of Puleo et al., *Biomaterials*, 23:2079-2087 (2002) (hereinafter "Puleo et al."). Applicants respectfully traverse the rejection.

As set forth above in detail, the combination of White et al. and Knopf et al. fails to render the scaffold of claim 10 obvious. Claim 19 depends from claim 10. Citation of Puleo et al. fails to remedy the deficiencies of the combination of White et al. and Knopf et al.

Puleo et al. was cited by the examiner as "teach[ing] a titanium implant on which was cross linked BMP-4 for the purpose of developing orthopedic and dental implants that induced bone formation…"

The combination of White et al., Knopf et al. and Puleo et al. fails to provide a scaffold with the characteristics of 1) immobilization of the peptide on the scaffold in an amount of 0.1-10 mg/cm^2, 2) addition of CGC spacer at the N-terminal end of the tissue growth factor-derived peptide, 3) the scaffold is an implant and the surface of the implant is modified by oxidation and nitrification to facilitate the adhesion of the active peptide to the surface.

Based on the foregoing, the combination of White et al., Knopf et al. and Puleo et al. fails to provide any logical basis for the scaffold recited in claim 19, dependent from claim 10. White et al., in view of Knopf et al. and Puleo et al. <u>does not</u> render the claimed invention obvious. Accordingly, withdrawal of the rejection of claim 19 under 35 U.S.C. § 103 as being obvious over White et al., in view of Knopf et al. and Puleo et al. is respectfully requested.

<u>CONCLUSION</u>

Based on the foregoing, all of applicants' pending claims 2, 3, 10-13, 19, 21 and 22 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the February 3, 2009 Office Action without extension was set at three months, or May 3, 2009. Applicants hereby request a three month extension of time under 37 C.F.R. § 1.136 to extend the deadline for response to and including August 3, 2009. Payment of the extension fee of <u>$555.00</u> specified in 37 C.F.R. § 1.17(a)(3), as applicable to small entity, is being made by on-line credit card authorization at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

Date: August 3, 2009

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Additional EFS Attachments:
Exhibits A-E
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Submission of Sequence Listing

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